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FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/421,778	FULLER, JAMES T.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11-17,20-23,25 and 28-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-17,20-23,25 and 28-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/26/04; 2/16/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on 12/6/04 has been entered.

Claims 1-8, 11-17, 20-23, 25 and new claims 28-41 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 102(e) as being anticipated by Gu et al. (U.S. Patent No. 6,200,751) is withdrawn because Gu fails to disclose a minimal promoter of the endothelial cell protein C binding protein (EPCR) because it is unclear which sequence would constitute a minimal EPCR promoter (This is also consistent with the Written Description Rejection below).

The rejection under 35 U.S.C. 102(b) as being anticipated by Deb et al. (J. Virology 66:6164-6170, 1992) is withdrawn because Deb fails to disclose a minimal promoter of the human proliferating cell antigen (PCNA) because it is unclear which sequence would constitute a PCNA minimal promoter (This is also consistent with the Written Description Rejection below).

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 11-13, 15-17, 20-21, 23, 25 and 28-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a modified rejection.***

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. "Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a method of obtaining expression of an antigen of interest in a mammalian subject, said method comprises transferring into cells of said subject a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the antigen, wherein said antigen is expressed in said mammalian cells in an amount sufficient to elicit an immune response to the antigen; a purified and isolated minimal promoter sequence; a vaccine composition comprising the same nucleic acid construct; coated particles suitable for use in particle-mediated nucleic acid immunization, which particles comprise carrier particles coated with the same nucleic acid construct; and a particle acceleration device loaded with the same coated particles. The instant claims encompass compositions and methods of uses

involving any minimal promoter sequence, and with respect to claims 13, 21 and 40 any functional variant of a minimal sCMV immediate early promoter sequence or any functional variant of a minimal PRV early promoter sequence.

Apart from disclosing the preparation of 3 human CMV (hCMV), simian CMV (sCMV) and pseudorabies virus (PRV) promoters represented by *Sal1/Bam1*, *Sal1/Sca1* and *Sal1/Not1* fragments of their respective enhanced promoters, the instant specification fails to describe and to provide a representative number of species for a broad genus of minimal promoter that has the same or similar functional properties as those described by the minimal hCMV, sCMV and PRV promoters (e.g., to express the coding sequence of an antigen in an amount sufficient to elicit an immune response to the antigen; particularly a dramatically increased antibody production relative to the enhanced promoters *in vivo*). The instant specification fails to teach which essential or critical elements that other minimal promoters or other functional variant of a minimal sCMV immediate early promoter or other functional variant of a minimal PRV early promoter need to possess in order to have the same functional properties as those of disclosed minimal hCMV, sCMV and PRV promoters. For example, what are the structural features and/or structural boundaries constituting a minimal promoter for human I-actin promoter, HSP70 promoter, human proliferating cell antigen (PCNA) promoter, and that these minimal promoters would have the same functional properties as those of minimal hCMV, sCMV and PRV promoters? And what are the structural features and/or structural boundaries constituting other functional variants for minimal sCMV and PRV promoters? The prior art at the effective filing date of the present

application does not provide description for such a broad genus of a minimal promoter contemplated by Applicant as evidenced by the teachings of Cochran (US Patent 5,047,237), Johnston et al. (U.S. Patent No. 6,194,389; IDS, AK-1), Fischer (U.S. Patent No. 6,156,567), Bujard et al. (U.S. Patent No. 5,888,981) and numerous other references cited below.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a representative species for a broad genus of a minimal promoter apart from the disclosed minimal hCMV, sCMV and PRV promoters to be utilized in the compositions and methods of uses as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Response to Arguments

Applicant's arguments related in part to the above rejection in the Amendment filed on 12/6/04 (pages 10-12) have been fully considered, but they are respectfully not found persuasive.

Applicant argues that that the examiner improperly requires the Applicant to describe features that do not form a part of a claim, such as features that result in "a dramatically increased antibody production relative to the enhanced promoters *in vivo*". Applicant further argues that a promoter is well known in the art as a segment of a nucleic acid to which a polymerase attaches, thereby aligning the polymerase so that transcription will initiate at a specific site in an operatively connected site; and that Applicant has described where the minimal promoter sequence is generally derived and how it can be isolated or produced. Applicant further cited on page 10, lines 17-26 and page 24, lines 8-14 where specific examples of minimal promoters are described.

Please note the Written Description rejection was made because a skilled artisan cannot envision the detailed structure of a representative species for a broad genus of **a minimal promoter** apart from the disclosed minimal hCMV, sCMV and PRV promoters to be utilized in the compositions and methods of uses as claimed. For example, what are the structural features and/or structural boundaries constituting a minimal promoter

for human I-actin promoter, HSP70 promoter, human proliferating cell antigen (PCNA) promoter, and that these minimal promoters would have the same functional properties as those of disclosed minimal hCMV, sCMV and PRV promoters? Additionally, what are the structural features and/or structural boundaries constituting other functional variants for minimal sCMV and PRV promoters? Which nucleotides to be deleted, substituted or inserted at which position(s) for these functional variants of minimal sCMV and PRV promoters? The rejection was based mainly on the failure of the instant specification to teach which essential or critical elements that constitute a broad genus of minimal promoters, apart from three specific disclosed minimal promoters.

Furthermore, please note that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Accordingly, claims 1-8, 11-12, 15-17, 20, 23, 25, 28, 33-41 are rejected under 35 U.S.C. 112, first paragraph, for the lack of Written Description for the reasons already set forth in the Office Action mailed on 8/27/03 (pages 2-5).

New claim 38 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

An embodiment of claim 38 is drawn to a vaccine composition containing a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for an antigen of interest, wherein the antigen is HIV antigen.

The specification teaches by exemplification the construction of Hepatitis B surface antigen (HbsAg) expression cassettes driven by full-length or minimal promoter systems (with or without enhancer, respectively) derived from simian CMV, human CMV and pseudorabies virus (PRV). The DNA constructs were coated onto gold carrier particles and administered to Balb/c mice using a particle-mediated delivery technique to the shaved bellies of the animals. Analysis of anti-HbsAg antibodies in sera taken from vaccinated mice six weeks later, revealed that minimal promoter system gave a significant improvement in antibody titer over the fully enhanced promoter system.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to a vaccine composition comprising a minimal promoter sequence operably linked to a coding sequence for an HIV antigen for the following

reasons. Please note that enablement requires the specification to teach how to make and **use** the claimed invention.

1. The breadth of the claim

An embodiment of claim 38 encompasses a vaccine composition containing any nucleic acid construct comprising any minimal promoter sequence operably linked to any coding sequence of an HIV antigen.

2. The state and the unpredictability of the art

The existence of an effective HIV vaccine was and continues to be elusive even several years after the effective filing date of the present application (Bojak et al., Drug Discovery Today 7:36-46, 2002; Mwau et al., J. Gene Medicine 5:3-10, 2003). There are several major scientific obstacles blocking the development of a successful preventive HIV vaccine. These include (1) the extraordinary variability of HIV strains which occur in different parts of the world over time and in patients, (2) the lack of an exact animal model of HIV-induced AIDS, and (3) the lack of understanding of correlates of positive immunity to HIV. Even in 2004, Desrosiers, R.C. (Nature Medicine 10:221-223, 2004) still state "Several lines of evidence indicate that development of an effective vaccine for HIV-1 is going to be, at best, extremely difficult. The inability to solve fundamental scientific questions is the root cause for why a successful vaccine is not currently within our grasp." (abstract). Pantaleo et al. (Nature Medicine 10:806-810, 2004) also state "The lack of understanding of some crucial scientific questions (such as how to generate neutralizing antibodies), the fact that current HIV vaccine candidates may not protect from infection, and the absence of definitive experimental evidence that

certain types of immune responses are indeed immune correlates of protection all favor the view that more basic research is needed before current vaccine candidates can be moved into large efficacy trials. However, it is also unclear what data from which animal model of HIV-1 infection are most relevant to human infection and vaccine protection." (page 809, col. 2, section entitled "Final considerations"). Therefore, it is apparent that the existence of an HIV vaccine remains elusive and unpredictable in 2004, let alone at the effective filing date of the presently claimed invention (10/19/1998).

Additionally, it is noted that at about the effective filing date of the present application Chattergoon et al. (FASEB J. 11:753-763, 1997; Cited previously) state that "Though DNA vaccines have shown promise in animal models and have raised hopes, the technology is considered an emerging technology" (column 1, paragraph 2, page 762). Leitner et al. (Vaccine 765-777, 2000; Cited previously) also state "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for the therapeutic vaccination of patients with infectious diseases or cancer in clinical trials" (see abstract). Moreover, McCluskie et al. (Mol. Med. 5:287-300, 1999) also state "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trials that have carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors." (column 2, last paragraph, page 296).

3. The amount of direction or guidance presented

Apart from the disclosing that a DNA construct containing a minimal promoter derived from simian CMV, human CMV or pseudorabies virus (PRV) operatively linked to a sequence encoding Hepatitis B surface antigen yields a significant improvement in antibody titer in mice over the respective fully enhanced promoter, the instant specification fails to provide sufficient guidance for a skilled artisan on how to obtain any prophylactic or protective effect specifically against an HIV antigen in a human host that is naturally infected by HIV. The simple increased anti-HbsAg antibody titer in sera taken from mice being vaccinated with a plasmid vector system containing a minimal promoter of the present invention is not reasonably correlated to any prophylactic or protective effect against HIV in the infected host, particularly in light of the state and the unpredictability of the HIV vaccine art discussed above. In 2004, Desrosiers, R.C. still state "First, we do not know how to elicit antibodies with potent neutralizing activity. Second, we do not know how to deal with the enormous sequence variability of the virus. Third, ...we do not understand the crucial components of the protective immune response...Finally, we do not know whether immunologic memory will ever be sufficient to protect against HIV-1. If it will not be sufficient, we need to learn how to elicit protective immune responses in a way that will persist." (page 222, col. 3, first paragraph).

Therefore, in light of the totality of the prior art on HIV vaccine at the effective filing date of the present application as discussed above, coupled with the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to **use** a vaccine composition as claimed.

4. Working example provided

There is an absence of an example demonstrating that any prophylactic or protective effect has been attained for any HIV vaccine composition as claimed.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the breadth of the claims, and the unpredictability of the relevant art on HIV vaccine, it would have required undue experimentation for one skilled in the art to make and **use** the instantly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 25 and 39-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Hofmann et al. (Proc. Natl. Acad. Sci. 93:5185-5190, 1996) for the same reasons already set forth in the Office Action mailed on 8/27/03 (pages 2-5).

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 12/6/04 (pages 15-16) have been fully considered, but they are respectfully not found persuasive.

Applicant argues mainly that Hoffman does not disclose, explicitly or inherently, the exclusion or removal of the native enhancer sequence from the promoter it discusses, hCMV. Additionally, Applicant argues that Hoffman suggests the potential interference of the viral enhancer and promoter with the PhCMV*-1 promoter is eliminated by the use of the mutant 3' LTR of pJrPro-in the SIN vector, which lacks the viral enhancer and promoter.

Please note that Hoffman teaches clearly a recombinant retroviral vector construct containing **a relatively weak minimal promoter $P_{hCMV*-1}$.** There is no evidence of record indicating or suggesting that the minimal promoter $P_{hCMV*-1}$ of Hoffman would contain **any endogenous CMV enhancer**. Please also note Hoffman refers to the potential interference of **Moloney viral enhancer and promoter elements** with the tet regulation of the **$P_{hCMV*-1}$** (page 5187, left column, bottom of the second paragraph), and that the term "minimal promoter" of the present invention encompasses the presence of a **heterologous enhancer** with the minimal promoter (see page 10, lines 10-13). Therefore, the recombinant retroviral vector construct of Hoffman meets the limitation of the "minimal promoter" as well as a functional variant of a hCMV immediate early minimal promoter or of the sequence spanning positions 0 to –118 of the hCMV immediate early minimal promoter.

Accordingly, claims 25 and 39-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Hofmann et al. (Proc. Natl. Acad. Sci. 93:5185-5190, 1996).

Claims 25 and 39-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Chao (U.S. Patent No. 6,368,825) for the same reasons already set forth in the Office Action mailed on 8/27/03 (page 17).

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 12/6/04 (page 19) have been fully considered, but they are respectfully not found persuasive.

Applicant argues mainly that Chao discloses promoters that have all or a portion of SEQ ID NO:2 removed from the full promoter resulting in SEQ ID NO:1, and that Chao does not disclose promoters where the native enhancer sequence is excluded. Therefore, Chao fails to disclose a vaccine composition comprising a minimal promoter sequence.

Once again, please note that for a composition claim the intended use is not given any patentable weight. In this instance, Chao teaches explicitly a recombinant baculovirus vector containing the 111 bp-minimal CMV promoter of SEQ ID NO:1 which is indistinguishable from a nucleic acid construct comprising a minimal promoter of the present invention. Furthermore, Applicant fails to provide any objective evidence

indicating that the 111 bp-minimal CMV promoter of SEQ ID NO:1 taught by Chao would contain any endogenous CMV enhancer element.

Accordingly, claims 25 and 39-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Chao (U.S. Patent No. 6,368,825) for the same reasons already set forth in the Office Action mailed on 8/27/03 (page 17).

Claims 1-3, 5-8, 12-14, 25 and 37-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Bujard et al. (U.S. Patent No. 5,888,981). ***This is a new ground of rejection with respect to the inclusion of claim 14.***

Bujard et al. disclose both *in vivo* and *ex vivo* methods for a regulated expression of a gene of interest in a cell in a subject, including human, using a tetracycline-controlled expression system (see abstract and cols. 27-33). The regulated expression system comprises a polynucleotide molecule encoding for a protein of interest, wherein the polynucleotide is operably linked to a tTA-responsive promoter that contains a minimal hCMV promoter (positions +75 to –53 to +75 to –31), and the protein of interest includes the X-protein of HBV (col. 23, lines 22-61), trans-dominant negative tat, rev and env mutants for HIV or transdominant Icp4 mutants for HSV (col. 28, lines 57-67), a viral protein such as adenovirus E19 protein (col. 32, lines 52-55). The expression of such proteins of interest in a subject in the absence of tetracycline would elicit an immune response to the proteins. Bujard et al. also teach the preparation of the minimal promoters hCMV-1* and hCMV*-2 (see col. 36, lines 44-60). Furthermore, the minimal promoters hCMV-1* and hCMV*-2 are functional variants of hCMV immediate

early minimal promoter or of the sequence spanning positions 0 to –118 of the hCMV immediate early minimal promoter. It is noted that a functional variant sequence may vary from a native promoter sequence by one or more base substitutions, deletions or insertions as taught by the instant application (see page 10, lines 27-28).

With respect to claims drawn to a vaccine composition, please note that for a composition claim its intended use is not given any patentable weight, particularly the nucleic acid constructs taught by Bujard et al are not distinguishable from the nucleic acid constructs in the vaccine composition of the present invention.

Accordingly, the teachings of Bujard et al. meet the limitation of the instant claims, and therefore Bujard et al. anticipates the instant claims.

Response to Arguments

Applicant's arguments related in part to the above rejection in the Amendment filed on 12/6/04 (page 18) have been fully considered, but they are respectfully not found persuasive.

Applicant argues mainly that the minimal promoters disclosed in Bujard are unable to activate transcription, and that a minimal promoter is defined by Bujard as a "partial promoter sequence which defines the transcription start site but which by itself is not capable, if at all, of initiating transcription efficiently" (col. 8, lines 36-41; col. 39, lines 42-45). Thus, Bujard fails to disclose or teach a minimal promoter sequence that initiates expression of the antigen in mammalian cells or a vaccine composition comprising a minimal promoter.

Please note that a "minimal promoter" as defined by the present application is simply an "enhancerless" promoter (page 4, lines 7-8). **There is no requirement that the minimal promoter is capable of initiating transcription efficiently**. As defined by Bujard, a minimal promoter is a partial promoter sequence which defines the transcription start site but which by itself is not capable of, if at all, of initiating transcription **efficiently**. The activity of such minimal promoters depend on the binding of activators such as tetracycline-controlled transactivator to operably linked binding sites (col. 8, lines 36-41). Therefore, the minimal promoters hCMV-1* and hCMV*-2 taught by Bujard meet the limitation of the instant claims since Bujard et al. disclose clearly both *in vivo* and *ex vivo* methods for a regulated expression of a gene of interest in a cell in a subject, including human, using a tetracycline-controlled expression system comprising the minimal promoters hCMV-1* and hCMV*-2. Furthermore, it should be noted that a minimal promoter of the present invention encompasses a promoter containing a heterologous enhancer (page 10, lines 10-13).

Accordingly, claims 1-3, 5-8, 12-13, 25 and 37-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Bujard et al. (U.S. Patent No. 5,888,981) for the reasons already set above.

Claims 1-8, 11-12, 15-17, 20, 23, 25, 28 and 33-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnston et al. (U.S. Patent No. 6,194,389; IDS, AK-1). ***This is a reinstated rejection.***

Johnston et al. disclose a method for obtaining a protective immune response in a vertebrate subject by *in situ* microprojectile bombardment by providing microprojectiles carrying a DNA sequence comprising in the 5' to 3' direction a regulatory element functional in the tissue cells and a gene positioned downstream of the regulatory element and under the transcriptional control thereof, the gene coding for a protective immune response-producing protein or polypeptide, wherein the microprojectiles comprise a material selected from the group consisting of metal (gold, tungsten, iridium), glass, silica, ice , polyethylene, polycarbonate, graphite and diamond; then accelerating the microprojectiles at the subject using a microprojectile acceleration cell transformation apparatus (See abstract, the claims and particularly col. 5 and 6). Johnston et al. teach that the regulatory sequences which may be used to provide transcriptional control of the gene in the polynucleic acid sequence are generally promoters which are operable in the target tissue cells, and that other regulatory elements which may optionally be incorporated into the polynucleic acid sequence include enhancers, termination sequences and others (col. 5, lines 42-45 and lines 65-67). The polynucleic acid sequence carried by the microprojectile is a recombinant construct of a gene and a regulatory element, which can be in the form of a plasmid (col. 4, lines 37-51). Exemplary promoters that Johnston et al. specifically teach include the human alpha-actin promoter of Miwa and Kedes (Mol. Cell Biol. 2803, 1987), the human beta-actin promoter, the troponin T gene promoter, the human heat shock protein 70 promoter, the metallothionin gene promoter among others. Additionally, exemplary of genes that code for proteins or peptides which produce an immune

response are genes encoding for subunit vaccines against enteroviruses, surface antigen of the hepatitis B (col. 5, lines 4-14). Johnston et al further teach to sugically expose the hypodermis and dermis by incision and blunt dissection of a skin flap from the animal and propel the microprojectiles directlyly into the hypodermis and dermis without projecting the microprojectiles through the outer surface layer, and then restoring the dissected skin flap (containing cells) to the position on the animal from which it came (col. 7, lines 53-67). The vertebrate subject or animal includes fish, reptiles and mammals such as horse, cow, sheep, pig and human (col. 4, lines 4-9).

It is noted that the claims recite a nucleic acid construct **comprising** a minimal promoter sequence operably linked to a coding sequence for an antigen, and therefore the nucleic acid construct is not necessarily limited only to a nucleic acid construct **consists of a minimal promoter sequence operably linked to a coding sequence for an antigen** as contemplated by Applicant because of the open term "comprising". Therefore, as written the claims also read over a nucleic acid construct containing other regulatory sequences including enhancers (both endogenous as well as heterologous enhancers) in addition to a "minimal promoter".

Accordingly, the teachings of Johnston et al. meet every limitation of the claims as written, and therefore Johnston et al. anticipate the instant claims.

Response to Arguments

Applicants' arguments related in part to the above rejection in the Amendment filed on January 29, 2002 in Paper No. 13 (pages 16-18) have been fully considered.

Applicant argues mainly that Johnston et al. do not teach the truncation or excision of enhancer sequences from the promoter systems described in their disclosure, and therefore Johnston et al. can not anticipate the presently claimed invention. Applicant further argues that all the claims include the limitation that a minimal promoter sequence is used to drive expression of the attached antigen sequence, and the term "minimal promoter" is clearly and unambiguously defined in the specification as only encompassing those promoters where the native enhancer has been excised or otherwise removed.

Examiner respectfully finds Applicants' argument to be unpersuasive because as already noted in the above rejection, as written the claims also read over a nucleic acid construct containing other regulatory sequences including enhancers (both endogenous as well as heterologous enhancers) in addition to a "minimal promoter". Should Applicant intend to claim a nucleic acid construct containing a minimal promoter, and said nucleic acid construct does not contain a native enhancer of said promoter, then Applicant should claim as such.

Accordingly, claims 1-8, 11-12, 15-17, 20, 23, 25, 28 and 33-39 are rejected for the reasons set forth above.

Claims 1-4, 7-8, 11-17, 20-23, 25, 29-30, 32-34, 36-37 and 39-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Lai et al. (DNA Cell Biol. 14:643-651, 1995; Cited previously). ***This is a reinstated rejection.***

Lai et al. disclose a vaccine DNA construct comprising a DNA fragment of *Mycoplasma pulmonis* encoding a protein recognized by a protective monoclonal antibody, under the control of the CMV immediate early promoter. Gold particles were coated with the vaccine DNA construct, and delivered directly into the skin of mice using a helium-driven, hand-held gene gun (column 2, first paragraph, page 645). Both humoral and cellular immunity were induced, and vaccinated mice were protected from infection upon challenges with *Mycoplasma pulmonis*.

Once again, due to the open language of the terms "comprising" as well as "consists essentially of" in the claims, the nucleic acid construct may contain enhancer elements (endogenous and/or heterologous enhancers) in addition to a minimal promoter sequence. Therefore, the CMV immediate early promoter in the DNA construct of Lai et al. contains the endogenous CMV minimal promoter sequence.

Accordingly, the teachings of Lai et al. meet all limitation of the instant claims, and thus the reference anticipates the instant claims as written.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on April 4, 2001 (pages 14-15) have been fully considered.

Applicant argues mainly that the term minimal promoter sequence is clearly and unambiguously defined in the specification as only those promoters where the native enhancer sequence has been excised or otherwise removed, and the vector construct described by Lai clearly includes a promoter sequence that is coupled with its native enhancer sequence. Therefore, the Lai reference could not anticipate any of Applicant's claims.

Examiner respectfully finds Applicant's argument to be unpersuasive because as already noted in the above rejection, as written the claims also read over a nucleic acid construct containing other regulatory sequences including enhancers (both endogenous as well as heterologous enhancers) in addition to a "minimal promoter". Should Applicant intend to claim a nucleic acid construct containing a minimal promoter, and said nucleic acid construct does not contain a native enhancer of said promoter, then Applicant should claim as such.

Accordingly, claims 1-4, 7-8, 11-17, 20-23, 25, 29-30, 32-34, 36-37 and 39-41 are rejected for the reasons set forth above.

Claims 1-4, 7-8, 11-17, 20-23, 25 and 28-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Haynes et al. (AIDS Res. Hum. Ret. 10, Supplement 2, pages S43-S45, 1994, IDS). ***This is a new ground of rejection.***

Haynes et al disclose Accell particle-mediated gene delivery of HIV-1 gp120 expression plasmid DNA-coated gold microparticles to mouse epidermis, and they found that low-level antigen expression in mouse skin generally results in modest gp120-specific igG antibody titers following three or four immunization, depending on the delivery voltage as well as cytotoxic cellular immune responses (see abstract and S44, right-hand column, top of last paragraph). Haynes et al also disclose that epidermal delivery of the various HIV-1 Gag-Pol-Env or Env vectors is driven by the human cytomegalovirus immediate early promoter (S44, right-hand column, top of last paragraph), and that the Accell gene delivery system employs a controlled electric discharge to create a shock wave that accelerates DNA coated gold particles into a given target tissue (S44, left-hand column, top of first paragraph).

Once again, due to the open language of the terms "comprising" as well as "consists essentially of" in the claims, the nucleic acid construct may contain enhancer elements (endogenous and/or heterologous enhancers) in addition to a minimal promoter sequence. Therefore, the CMV immediate early promoter in the plasmid DNA construct of Haynes et al also contains the endogenous CMV minimal promoter sequence. With respect to claims drawn to a vaccine composition, please note that for a composition claim its intended use is not given any patentable weight, particularly the expression plasmid DNA taught by Haynes et al is not distinguishable from the nucleic acid construct in the vaccine composition of the present invention.

Accordingly, the teachings of Haynes et al. meet all limitation of the instant claims, and thus the reference anticipates the instant claims as written.

Claims 1-3, 7-8, 12-13, 25, 37 and 39-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Cochran (US Patent 5,047,237). ***This is a new ground of rejection.***

Cochran discloses a vaccine comprising an effective immunizing amount of an attenuated pseudorabies virus (PRV) and a method of immunizing an animal such as swine, bovine, dog and cat against pseudorabies virus by administering (e.g., inoculating intramuscularly) to the animal an effective immunizing amount of the attenuated pseudorabies virus (see abstract; col. 7, lines 4-27; and col. 14, lines 53-55).

Once again, due to the open language of the terms "comprising" as well as "consists essentially of" in the claims, the nucleic acid construct may contain enhancer elements (endogenous and/or heterologous enhancers) in addition to a minimal promoter sequence. Therefore, an attenuated pseudorabies DNA virus of Cochran also contains a minimal endogenous PRV early promoter region. With respect to claims drawn to a vaccine composition, please note that for a composition claim its intended use is not given any patentable weight, particularly the attenuated PRV taught by Cochran is not distinguishable from the nucleic acid construct in the vaccine composition of the present invention.

Accordingly, the teachings of Cochran meet all limitation of the instant claims, and thus the reference anticipates the instant claims as written.

Claims 1-3, 7-8, 12-14, 25, 28 and 37-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Fischer (U.S. Patent No. 6,156,567). ***This is a new ground of rejection.***

Fischer discloses a recombinant canine adenovirus (CAV) containing a truncated transcriptionally active cytomegalovirus immediate early promoter (e.g., a 91 base pairs in length of human CMV-IE as shown in Figure 20; a 145 base pairs in length of human CMV-IE as set forth in Figure 13C; or a 466 base pairs in length of murine CMV-IE) operably linked to an exogenous DNA, wherein the DNA encodes an antigen of a human pathogen such as a Hepatitis virus antigen (e.g., HbsAg) or HIV antigen such as gp120, gp160 and others (col. 8, line 60 continues to line 51 of col. 10; col. 13, line 5 continues to line 62), as well as an immunogenic or vaccine composition containing the same (col. 11, lines 7-21). Fischer further teaches a method of inducing an immunological response in a host vertebrate, including humans, comprising administering to the host the same immunogenic or vaccine composition (col. 11, line 22 continues to line 44) by parenteral, subcutaneous, intradermal, intramuscular or intravenous injection (col. 30, lines 33-42). Fischer teaches specifically that a truncated promoter can be as little as 10% of the original base pairs of the full-length promoter (col. 13, lines 37-39; col. 15, line 31 continues to line 45 of col. 16). With respect to claims drawn to a vaccine composition, please note that for a composition claim its intended use is not given any patentable weight, particularly the recombinant canine adenovirus taught by Fischer is not distinguishable from the nucleic acid construct in the vaccine composition of the present invention.

Accordingly, the teachings of Fischer meet all limitation of the instant claims, and thus the reference anticipates the instant claims as written.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Quang Nguyen, Ph.D.

QUANG NGUYEN, PH.D
PATENT EXAMINER